Testicular Regression Syndrome
A Case Report

Francesco Corrado, M.D.
Narcisio Carlo Stella, M.D.
Onofrio Triolo, M.D.

Testicular regression syndrome occurred in a 20-year-old, white, phenotypic female with a 46,XY karyotype. The basal levels of serum gonadotropins were elevated, while the testosterone was in the normal range. Estrogens were undetectable. At laparotomy no gonadal rudiments or müllerian or wolffian derivatives were found. The logical diagnosis was late embryonic testicular regression with a specific testicular insult 62–63 days after fertilization.

From the Department of Obstetrics and Gynecology, University of Messina, Messina, Italy.

Address reprint requests to: Francesco Corrado, M.D., Istituto di Ginecologia, Policlinico Universitario, 98100 Messina, Italy.

Introduction

Women with a female phenotype but who are X-chromatin negative and without any recognizable gonadal tissue or development of the internal genitalia were first described by Overzier and Linden in 1956[1]; they called this syndrome "true agonadism." Since then about 20 cases,[2-15] with different nomenclature and a broad range of sexual duct development after puberty, have been reported. In 1977 Edman suggested the term *embryonic testicular regression syndrome* to indicate that the intrauterine defect occurs early in male embryogenesis. An absence of müllerian and wolffian derivatives was seen in the case described below.

Case Report

A 20-year-old, white, phenotypic female, gravida 0, para 0, was referred to our institute for an evaluation for primary amenorrhea and sexual infantilism. The patient was the second child of unrelated parents, born at term after an uncomplicated pregnancy; the first child was without reproductive problems. The patient denied having headaches, visual disturbances, sexual activity, galactorrhea, abnormal eating habits, wide fluctuations in weight, constitutional symptoms or psychologic-emotional dysfunction, or the use of medication.[5]

On the physical examination the patient appeared obese (weight, 90 kg; height, 168 cm), with undeveloped breasts (Tanner II) and absent pubic and axillary hair. The external genitalia were markedly hypoplastic. The vagina was 3 cm long, with a blind end. No inguinal or labial masses were palpable. A rectal examination failed to demonstrate the presence of a uterus or gonads. An endocrine examination under basal conditions revealed elevated plasma gonadotropin levels (follicle stimulating hormone, 106 mIU/mL; luteinizing hormone, 81 mIU/mL) and low serum testosterone values (0.2 ng/mL). The PRL level was 18 ng/mL, and estrone and estradiol were undetectable. The intramuscular administration of human chorionic gonadotropin (5,000 U/d) for three days resulted in no important change in the serum testosterone levels (0.2–0.5 ng/mL).

Ultrasonography of the pelvis did not demonstrate ovaries or a uterus. An intravenous pyelogram demonstrated a normal urinary system. Cytogenetic investigations from peripheral blood lymphocyte cultures showed a 46,XY karyotype, confirmed by R (RBG), C (CBG) and Q (QFQ) banding. At laparoscopy neither a uterus, fallopian tubes, wolffian derivatives or gonadal rudiments were found in the pelvis.

0024-7758/91/3607-0549/$1.50/0

The patient began estrogen therapy (1.25 mg/d) for breast growth, but her parents refused surgical treatment (vaginoplasty).

Discussion

Sexual development is a sequential, ordered and relatively simple process. The presence of an X or Y chromosome causes differentiation of the gonads into testes or ovaries. Y chromosome function appears first at eight weeks of gestation, mediated by the presence of a cell surface antigen (HY) that induces the transformation of the genital ridge into testes. The critical role of the testes in male phenotypic differentiation consists of two fundamentally distinct and sequential processes: (1) regression of the müllerian ducts, mediated by the müllerian inhibition factor, and (2) virilization of the wolffian ducts and urogenital sinus by androgens.

A critical insult to the testes during embryogenesis results in the testicular regression syndrome, which is characterized by the absence of functional gonads in an XY individual. This rare syndrome is represented by a wide spectrum of clinical features, extending from a phenotypic female with streak gonads, hypoplastic uterus and external hypoplastic female genitalia (Swyver's syndrome) to an anorchic, phenotypic male. The manifestation depends on the time of the testicular regression.

In our case the female phenotype, development of the lower two-thirds of the vagina and absence of internal genitalia and gonadal elements suggest that the testicular injury may have occurred about 62 days after fertilization. The critical insult probably occurred after the müllerian regression factor began functioning (60–61 days after fertilization) but before testosterone synthesis (68–70 days). The same timing was present in the other nine reported cases with no evidence of müllerian or wolffian derivatives. That is the most frequent phenomenon with this syndrome. Different timing probably occurred, in the presence of various degrees of müllerian duct rudiments, in the cases reported by Overzier,[1] DeWursht,[4] Sarto,[5] Penney,[9] Coulam[11] and De Marchi.[12] The testicular damage seems to have occurred earlier in the cases reported by the last two authors, whereas it probably occurred later in Rosemberg's case,[13] the only one in which the presence of wolffian derivatives suggested that androgen synthesis had just begun.

In our patient no family history existed to substantiate the theory that the syndrome was genetically transmitted.

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